

REMARKS

Upon entry of the present amendment, claims 1-26, 28, 29, and 31-36 will be pending in the present application. Claims 1-22, 30, and 31 are withdrawn, leaving claims 23, 26, 28-29 and 32-36 under consideration. Applicants have amended claims 23, 28 and 31, and cancelled claims 27 and 30. Support for these amendments can be found throughout the application as filed, e.g., at page 4, lines 29-30; page 14, lines 24-26; page 38, lines 5-9; and the claims as filed, e.g., claim 27, *inter alia*. No new matter has been added.

Rejection under 35 U.S.C. 112, First Paragraph

The sole remaining rejection in the present case is for an alleged lack of enablement of the claimed methods. The Office Action mailed October 5, 2006 ("the Office Action"), alleges that the specification

... fails to provide any relevant teachings or specific guidance or working examples with regard to transducing a blood cell *ex vivo* with wnt5a and/or obtaining any blood cells from a subject, transduce cells *ex vivo* with wnt5a, reintroduce the cells into the subject wherein therapeutic levels of the transgene are produced resulting in the treatment of a subject with Wnt5a hematopoietic cancer.

In addition, the Office Action alleged that the specification "failed to provide specific guidance or working examples correlating to treatment of any Wnt5a hematopoietic cancer by the claimed method...". (see page 5 of the Office Action).

Applicants respectfully traverse.

Applicants note that the Examiner's concern with the difficulties associated with cell therapy in general appears to be based on publications that have little relevance to the pending claims. For example, the Examiner cites Gage et al. at page 20, 2nd column, for the proposition that the number of cells needed to perform the desired function may be a limiting factor. However, this is a general statement regarding cell therapies, and as Gage et al. themselves note (and Applicants previously stated), as few as 3.5×10^3 stem cells are sufficient to completely reconstitute all compartments of the hematopoietic system, a relatively low number. However,

applicants note that the present methods do not require the complete destruction and reconstitution of the hematopoietic system. The present methods provide a way to suppress proliferation of Wnt5a-negative cells by administering blood cells that secrete Wnt5a, providing to those Wnt5a-negative cells the missing Wnt5a protein, thereby inhibiting proliferation of the Wnt5a-negative cells. Even if complete destruction and reconstitution was desired, one of skill in the art would appreciate that bone marrow transplants are routine in the art; they are a standard treatment modality and the issues associated with cell sources and protocols are well-understood.

The Scanlon reference cited at page 6 of the Office Action relates only to challenges associated with cell therapy in general, most of which are simply not applicable in the present case, e.g., concerns about repopulating the host, determining cell type, and DNA repair genes. The Becker reference is cited at page 6 of the Office Action for noting that one problem with CD34 selection is that only a small subset of CD34+ cells fulfill the definition of stem cells. However, the pending claims do not require the use of CD34 as a selection criterion, as any blood cell can be used; therefore, this concern is also irrelevant to the claimed methods. Again, the cells useful in the present methods are not limited to stem cells; other blood cells, such as B or T cells, are also expected to work, and to provide sufficient Wnt5a to reduce proliferation of leukemia and lymphoma cells as claimed (see the discussion below, and the Declaration of Stephen Jones, Ph.D. (the "Declaration"), submitted herewith).

The Examiner also cited the abstract of Kohn et al., 2001, at page 6 of the Office Action, noting that "inefficient gene transfer to human hematopoietic stem cells has imposed the major limitation to successful application of gene therapy." This statement was taken out of context, and its function as simply an introductory remark becomes apparent from a reading of the full article. Applicants submit herewith the entire text of the Kohn et al. reference, and note that the reference details a number of methods for enhancing gene transfer and expression (see pages 383-385). Furthermore, as applicants note above, the methods are not limited to stem cells, and the specification itself includes examples of successful expression in B cells transduced with Wnt5a retrovirus (see the discussion below, and the Declaration, submitted herewith).

Applicants note that many of the diseases for which difficulties are cited are ones in which substantially all of the defective cells must either be eradicated or genetically modified, e.g., SCID, which must have a sufficient number of transduced progenitors to produce functional

T cells; Fanconi's anaemia, in which the DNA repair response must be reconstituted; and Gaucher's disease, in which a deficiency of glucocerebrosidase activity results in lipid storage in tissue macrophages. However, this is not the case in the present methods, as Wnt5a acts extracellularly, and thus a small population of transduced cells secreting Wnt5a can reasonably be expected to rescue the Wnt5a-negative cells.

Finally, the cautionary tale told in the Budak-Alpdogan et al. reference cited at pages 6-7 of the Office Action relates to viral integration at an inappropriate site. The fact that there may be side effects (which Applicants specifically do not concede) is not relevant to patentability. MPEP § 2164.05 states that "Considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ('Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].')." Furthermore, one of skill in the art will appreciate that the risk of such adverse outcomes can be minimized by careful selection of a vector for delivery of the nucleic acid encoding Wnt5a.

The Office Action noted further at page 9 that "[w]hat is contested is not the methodology of cell based gene therapy rather the unpredictability of a correlation between of the execution of the methodology and the effect resulting in the treatment of a Wnt5a associated hematopoietic cancer."

Per MPEP 2164.02, an applicant need not have actually reduced the invention to practice prior to filing. The Federal Circuit has blessed reliance on *in vitro* data in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

... "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

In this case, the desired "pharmacological activity" is a decrease in cellular proliferation in cells that have lost Wnt5a, to treat leukemia or non-Hodgkin's lymphoma. The *in vitro* examples presented in the specification demonstrate that expressing Wnt5a in these cells reduces proliferation. Thus, there is a direct correlation between the disclosed *in vitro* utility and *in vivo* activity.

As noted at paragraph 3 of the Declaration attached hereto, the specification provides examples of

... transducing two separate B cell lines with a retroviral construct that includes a Wnt5a coding sequence. Page 49, line 20 to page 50, line 7, of the application describes experiments in which 7C6 and 1-8 B cells, which are Abelson leukemia virus-transformed B cells lines that lack Wnt5a expression, were transformed with a retroviral construct encoding Wnt5a. Figure 21 of the application shows Wnt5a expression only in those cells transduced with the Wnt5a vector, and none in those cells transduced with an empty vector. These results clearly demonstrate expression of Wnt5a in transduced blood cells.

As Dr. Jones explains at paragraph 4, these cells produce levels of Wnt5a that are able to suppress proliferation:

4. As is also demonstrated in Figure 21, cyclin D levels were greatly reduced in those cells transduced with the Wnt5a virus. Cyclin D levels correspond with cell proliferation, thus a decrease in Cyclin D is associated with a decrease in cell proliferation. This is demonstrated in Figure 23, which shows a decrease in BrdU uptake in cells transduced with the Wnt5a virus. Reduced BrdU uptake indicates reduced cell proliferation, thus, expression of Wnt5a by transduced cells results in the desired pharmacological outcome: suppression of proliferation.

These experiments provide evidence of *in vitro* activity that one of skill in the art would reasonably expect to correlate with *in vivo* activity, as Dr. Jones notes at paragraph 5:

These cell lines are derived from B cells and are widely accepted models of leukemic cells, and, like the blood cells of the patients with B cell lymphoma described in Example 10 (see pages 51-53) of the present application, lack Wnt5a. The experiments in the present specification demonstrate that expression of Wnt5a in B cells results in a decrease in cell proliferation.

One of skill in the art would reasonably believe that this effect, which is demonstrated so clearly *in vitro*, would also occur *in vivo*.

In addition, applicants have expressed Wnt5a in NFC cells, a CD4+CD8+ T cell line that lacks endogenous Wnt5a expression. As Dr. Jones notes at paragraph 6,

... NFC-WNT5a cells grew significantly slower in culture than NFC cells transduced with control empty vector (see Figure B). Expression of exogenous Wnt5a also suppressed the level of Cyclin D1 in NFC cells, confirming that Wnt5a can potentially regulate cell cycle progression of DP thymocytes (Figure C). Furthermore, the level of apoptosis following serum withdrawal was elevated in cells expressing Wnt5a relative to the levels of apoptosis in control

NFC cells (Figure D). Finally, transduction of Wnt5a upregulated levels of the proapoptotic protein Bax, (Figure E) concomitant with a 4-fold increase in Bax gene expression (Figure F), confirming that Wnt5a is pro-apoptotic in thymocytes.

Dr. Jones concludes that

These results indicate that Wnt5a inhibits the proliferation of cells from different hematopoietic compartments: T cells and B cells, and thus can be expected to be useful in inhibiting proliferation of hematopoietic cancers associated with aberrant proliferation of those cells, i.e., leukemia and non-Hodgkin's lymphoma.

These results, Applicants submit, provide ample evidence that the claimed methods will work across the range of claimed diseases.

Furthermore, the Examiner's concern regarding achieving therapeutic levels of Wnt5a is answered by those same experiments, in which levels of Wnt5a expressed from a retroviral vector are sufficient to decrease proliferation in leukemia cells (see Figure 23 of the application as filed, and Figure B of the Declaration). One of skill in the art would be able to increase or decrease the amount of suppression as needed by selection of promoters that result in increased or decreased expression; such manipulations are well within the skill of the art. Thus, one of skill in the art would readily be able to determine an appropriate dose; this is no more than routine in the art of treating subjects with hematopoietic cancers such as those recited in the present claims.

For at least these reasons, applicants submit that the claims as amended are amply enabled. Applicants request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn and the claims allowed.

Applicant : Jones et al.
Serial No. : 10/719,054
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Conclusion

Early and favorable action is therefore requested. If the Examiner feels that it would further prosecution of the present application, she is invited to telephone the undersigned at (617) 956-5985.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-178001.

Respectfully submitted,

Date:

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